Docket No. 46528/102/JOHO

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

CANCER CHEMOPROTECTIVE FOOD PRODUCTS

the specification of which (check one)

☒ is attached hereto

☐ was filed on as Application Serial No. and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)

NUMBER	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Stephen A. Bent, Reg. No. 29,768; David A. Blumenthal, Reg. No. 26,257; John J. Feldhaus, Reg. No. 28,822; Donald D. Jeffery, Reg. No. 19,980; Eugene M. Lee, Reg. No. 32,039; Peter G. Mack, Reg. No. 26,001; Brian J. McNamara, Reg. No. 32,789; Sybil Meloy, Reg. No. 22,749; George E. Quillin, Reg. No. 32,792; Colin G. Sandercock, Reg. No. 31,298; Bernhard D. Saxe, Reg. No. 28,665; Richard L. Schwaab, Reg. No. 25,479; Arthur Schwartz, Reg. No. 22,115; Harold C. Wegner, Reg. No. 25,258.

Send all correspondence to FOLEY & LARDNER, 3000 K Street, N.W., Suite 500, Washington, DC 20007-5109. Address telephone communications to *Bernhard D. Saxe* at (202) 672-5300.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole Inventor	Signature of First or Sole Inventor	Date
Jed W. FAHEY	Jed W. Fahey	1/13/95
Residence Address		**Country of Citizenship**
6704 RIDGE RD., ELDERSBURG, MD 21784		*United States*
Post Office Address		
6704 RIDGE RD., ELDERSBURG, MD 21784		

Signatures should conform to names as typewritten. ☒ Additional inventors on attached Page 2.

Full Name of Second Inventor	Signature of Second Inventor	Date
Paul TALALAY	Paul Talalay	9/13/95
Residence Address	**Country of Citizenship**	
5512 BOXHILL LANE, BALTIMORE MD 21210	*United States*	
Post Office Address		
5512 BOXHILL LANE BALTIMORE MD 21210		

Applicant or Patentee: I EY et al.
Serial or Patent No.: ~~08/528,858~~ Atty. Dkt. No. 0528/102/JOHO
Filed or Issued: ~~9/15/95~~
For: CANCER CHEMOPROTECTIVE FOOD PRODUCTS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27 (c)) — NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION: Johns Hopkins School of Medicine
ADDRESS OF ORGANIZATION: 2024 E. Monument Street, Suite 2-100, Baltimore, MD 21205
TYPE OF ORGANIZATION:
(X) UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
( ) TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) AND 501(c)(3))
( ) NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
(NAME OF STATE)
(CITATION OF STATUTE)
( ) WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3) IF LOCATED IN THE UNITED STATES OF AMERICA
( ) WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
(NAME OF STATE)
(CITATION OF STATUTE)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) or (b) of Title 35, United States Code with regard to the invention entitled CANCER CHEMOPROTECTIVE FOOD PRODUCTS by inventor(s) FAHEY *et al.* described in

(X) the specification filed herewith
( ) application serial no. _____, filed _____
( ) patent no. _____, issued _____

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above-identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME:
ADDRESS:
0 INDIVIDUAL 0 SMALL BUSINESS CONCERN 0 NONPROFIT CORPORATION

NAME:
ADDRESS:
0 INDIVIDUAL 0 SMALL BUSINESS CONCERN 0 NONPROFIT CORPORATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate: (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: David A. Blake, Ph.D.
TITLE OF PERSON OTHER THAN OWNER: Executive Vice Dean
ADDRESS OF PERSON SIGNING: 3720 Rutland Avenue, Baltimore, Maryland 21205
SIGNATURE: _____ DATE: _____

08997813 • 122497

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MARCH 14, 1996

PTAS

100091892A

B SAXE
FOLEY & LARDNER
P.O. BOX 25696
3000 K STREET, N.W., SUITE 500
WASHINGTON, D.C. 20007-5109

RECEIVED
MAR 20 1996
FOLEY & LARDNER

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231.

RECORDATION DATE: 09/15/1995 REEL/FRAME: 7694/0746
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
FAHEY, JED W. DOC DATE: 09/13/1995

ASSIGNOR:
TALALAY, PAUL DOC DATE: 09/13/1995

ASSIGNEE:
JOHNS HOPKINS SCHOOL OF MEDICINE
2024 E. MONUMENT STREET, SUITE 2-100
BALTIMORE, MARYLAND 21205

SERIAL NUMBER: 08528858 FILING DATE: 09/15/1995
PATENT NUMBER: ISSUE DATE:

SEDLEY PYNE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

08528858 ET87/6680

JHU-TECHNOLOGY LICENSING TEL: 410-955-1245 Apr 4.97 15:13 No.006 P.03

9-15-95

11-21-1995

FORM PTO-1595 modified (Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

RECORDATION FORM COVER SHEET PATENTS ONLY

SEP 15 1995

U.S. DEPARTMENT OF COMMERCE Patent and Trademark Office

11/15/95

100091898

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies): Jed W. FAHEY, Paul TALALAY Additional name(s) of conveying party(ies) attached? No	2. Name and address of receiving party(ies): Name: Johns Hopkins School of Medicine Internal Address: Street Address: 2024 E. Monument Street, Suite 2-100 City: Baltimore, State: MD ZIP: 21205 Additional name(s) & address(es) attached? No
3. Nature of conveyance: XX Assignment / Merger Security Agreement / Change of Name Other Execution Date: 09-13-95	

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: 09-15-95

A. Patent Application No.(s)

B. Patent No.(s)

Additional numbers attached? No

5. Name and address of party to whom correspondence concerning document should be mailed: Name: FOLEY & LARDNER - Attn: B. Saxe Internal Address: P.O. Box 25696 Street Address: 3000 K Street, N.W., Suite 500 City: Washington, D.C. ZIP: 20007-5109	6. Total number of applications and patents involved: 1 7. Total fee (37 C.F.R. § 3.41)........$40.00 XX Enclosed _ Authorized to be charged to deposit account 8. Deposit account number: (Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

110 MG 10/11/95 08528858 1 581 40.00 CK

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Bernhard D. Saxe — Name of Person Signing

Signature

September 15, 1995 — Date

Total number of pages including cover sheet, attachments, and document: 2

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

08/527,869

A ;IGNMENT - WORLDV DE

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto

JOHNS HOPKINS SCHOOL OF MEDICINE

its successors and assigns, the entire right, title and interest, so far as concerns the United States and the Territories and Possessions thereof and all foreign countries in and to the invention in

CANCER CHEMOPROTECTIVE FOOD PRODUCTS

as set forth in his United States Patent Application

XX executed concurrently herewith
_ executed on ________________
_ Serial No. ________ filed ____________

said application for United States Letters Patent, including all divisional, renewal, substitute, continuation and Convention applications based in whole or in part upon said inventions or upon said applications, and any and all Letters Patent and reissues and extensions of Letters Patent granted for said inventions or upon said applications and every priority right that is or may be predicated upon or arise from said inventions, said applications, and said Letters Patent; said Assignee being hereby authorized to file patent applications in any or all countries on any or all said inventions in the name of the undersigned or in the name of said Assignee or otherwise as said Assignee may deem advisable, under the International Convention or otherwise; the Commissioner of Patents and Trademarks of the United States of America being hereby authorized to issue or transfer all said Letters Patent to said Assignee in accordance herewith; this assignment being under covenant, not only that full power to make the same is had by the undersigned, but also that such assigned right is not encumbered by any grant, license, or other right theretofore given, and that the undersigned will do all acts reasonably serving to ensure that the said inventions, patent applications and Letters Patent shall be held and enjoyed by said Assignee as fully and entirely as the same could have been held and enjoyed by the undersigned if this assignment had not been made, and particularly to execute and deliver to said Assignee all lawful documents including petitions, specifications, oaths, assignments, invention disclaimers, and lawful affidavits in form and substance which may be requested by said Assignee, to furnish said Assignee with all facts relating to said inventions or the history thereof and any and all documents, photographs, models, samples or other physical exhibits which may be of said inventions, and to testify in any proceedings relating to said inventions, patent applications and Letters Patent.

The undersigned hereby grant the firm of FOLEY & LARDNER the power to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

NAMES AND SIGNATURES OF INVENTORS		
Name: Jed W. FAHEY	Signature: Jed W. Fahey	Date: 9/13/95
Name: Paul TALALAY	Signature: Paul Talalay	Date: 9/13/95
Name:	Signature:	Date:
NAMES AND SIGNATURES OF WITNESSES		
Name: RUTH DILLINGER	Signature: Ruth Dillinger	Date: 9/13/95
Name: SHARON KERRY	Signature: S. Kerry	Date: 9-13-95

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.

IPT-407:4/90(1)(modified)

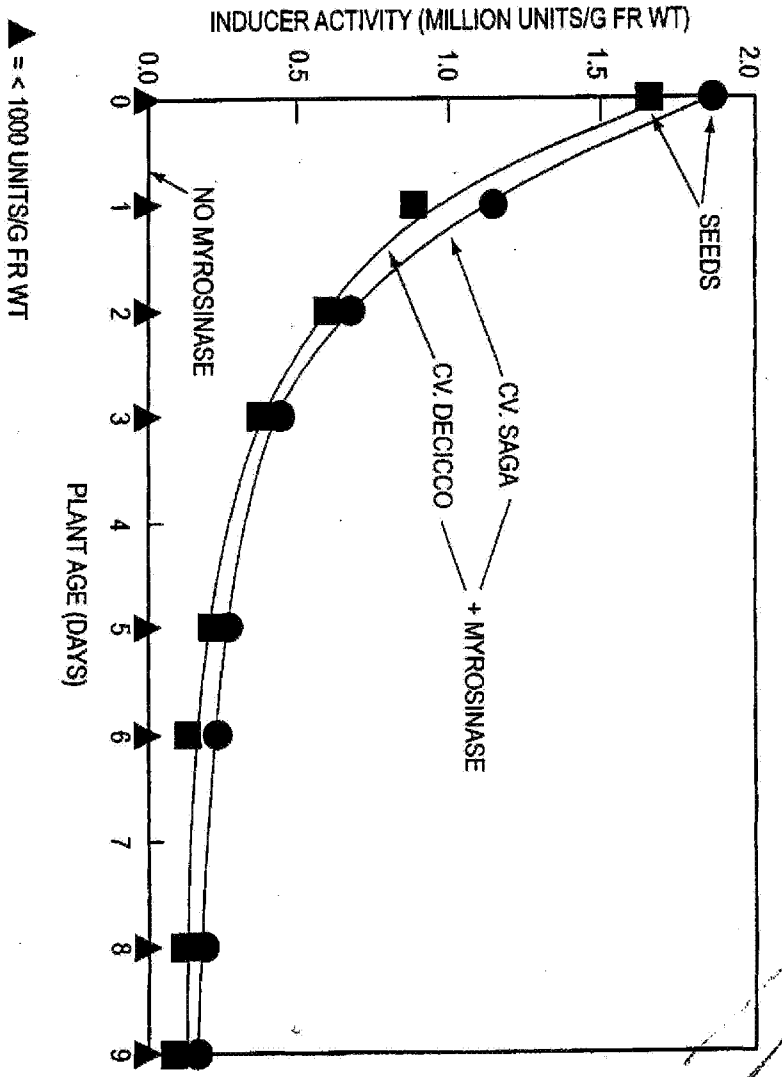
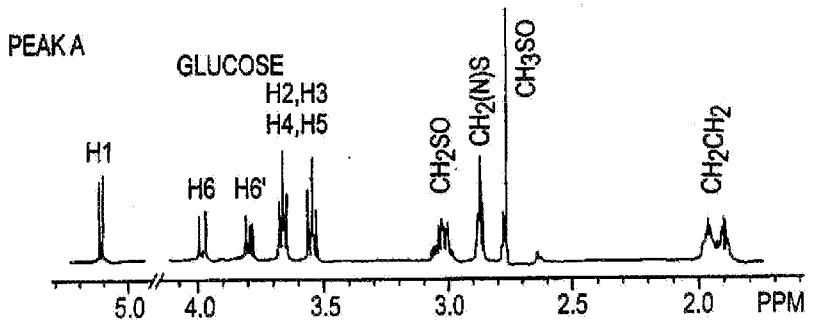


FIG. 1

08997813.122497

FIG. 2A


PEAK A
GLUCOSE
H2,H3
H4,H5
H1
H6
H6'
CH2SO
CH2(N)S
CH3SO
CH2CH2
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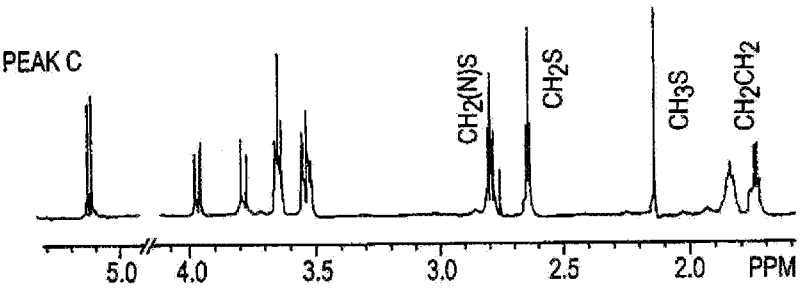
4.0
3.5
3.0
2.5
2.0
PPM

FIG. 2B


PEAK C
CH2(N)S
CH2S
CH3S
CH2CH2
5.0
4.0
3.5
3.0
2.5
2.0
PPM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 046528/0116/JOHO

In re patent application of
Jed FAHEY *et al.*
Serial No. Unassigned
Filed: Concurrently herewith
For: CANCER CHEMOPROTECTIVE FOOD PRODUCTS

(Divisional of Serial No. 08/528,858, filed Sept. 15, 1995)

PRELIMINARY AMENDMENT

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Preliminary to examination please amend the above-identified application as follows:

IN THE CLAIMS:

Kindly cancel claims 1-47 without prejudice and disclaimer and add the following new claims:

--48. A method of increasing the chemoprotective amount of Phase 2 enzymes in a mammal, comprising the step of administering to a mammal an effective quantity of cruciferous sprouts, with the exception of *Brassica oleracea capitata*, *Lepidium sativum*, *Sinapis alba*, *Sinapis nigra*, and *Raphanus sativus* sprouts, harvested between the onset of germination up to and including the 2-leaf stage, or a non-toxic solvent extract of said sprouts.

~~49~~. The method according to claim 48, wherein said sprouts are harvested 1 to 14 days post-germination and have at least 200,000 units per gram fresh weight of Phase 2 enzyme-inducing potential when measured after 3-days of growth from seeds that produce said sprouts and non-toxic levels of indole

glucosinolates and their breakdown products and goitrogenic hydroxybutenyl glucosinolates.

8 ~~50~~. The method according to claim 1 ~~49~~, wherein said sprouts are a *Brassica oleracea* selected from the group of varieties consisting of *acephala, alboglabra, botrytis, costata, gemmifera, gongylodes, italica, medullosa, palmifolia, ramosa, sabauda, sabellica, and selensia.*

9 ~~51~~. The method according to claim 8 ~~50~~, wherein said sprouts are a *Brassica oleracea* variety *italica*.

10 ~~52~~. The method according to claim 8 ~~50~~, wherein said sprouts are a *Brassica oleracea* variety *botrytis*.

11 ~~53~~. The method according to claim 10 ~~52~~, wherein said sprouts are a *Brassica oleracea* variety *botrytis* subvariety *cauliflora*.

12 ~~54~~. The method according to claim 1 ~~48~~, wherein said sprouts are substantially free of Phase 1 enzyme-inducing potential.

13 ~~55~~. The method according to claim 1 ~~48~~, wherein said non-toxic solvent extract is water.

14 ~~56~~. The method according to claim 1 ~~48~~, wherein said non-toxic solvent extract further comprises a cruciferous vegetable comprising an active myrosinase enzyme.

15 ~~57~~. The method according to claim 14 ~~56~~, wherein said cruciferous vegetable comprising an active myrosinase enzyme is of the genus *Raphanus*.

58. A method of increasing the chemoprotective amount of Phase 2 enzymes in a mammal, comprising the step of administering

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47

to a mammal an effective quantity of a food product comprising cruciferous sprouts, with the exception of *Brassica oleracea capitata*, *Lepidium sativum*, *Sinapis alba*, *Sinapis nigra*, and *Raphanus sativus* sprouts, harvested between the onset of germination up to and including the 2-leaf stage, or a non-toxic solvent extract of said food product.

59. The method according to claim 58, wherein said sprouts have at least 200,000 units per gram fresh weight of Phase 2 enzyme-inducing potential when measured after 3-days of growth from seeds that produce said sprouts and non-toxic levels of indole glucosinolates and their breakdown products and goitrogenic hydroxybutenyl glucosinolates and are harvested 1 to 14 days post-germination.

60. The method according to claim 58, wherein said sprouts are a *Brassica oleracea* selected from the group of varieties consisting of *acephala*, *alboglabra*, *botrytis*, *costata*, *gemmifera*, *gongylodes*, *italica*, *medullosa*, *palmifolia*, *ramosa*, *sabauda*, *sabellica*, and *selensia*.

61. The method according to claim 60, wherein said sprouts are a *Brassica oleracea* variety *italica*.

62. The method according to claim 60, wherein said sprouts are a *Brassica oleracea* variety *botrytis*.

63. The method according to claim 62, wherein said sprouts are a *Brassica oleracea* variety *botrytis* subvariety *cauliflora*.

64. The method according to claim 58, wherein said sprouts are substantially free of Phase 1 enzyme-inducing potential.

65. The method according to claim 58, wherein said non-toxic solvent extract is water.

66. The method according to claim 58, wherein said non-toxic solvent extract further comprises a cruciferous vegetable comprising an active myrosinase enzyme.

67. The method according to claim 66, wherein said cruciferous vegetable comprising an active myrosinase enzyme is of the genus *Raphanus*.

68. A method of reducing the level of carcinogens in a mammal, comprising administering to a mammal an effective amount of cruciferous sprouts, with the exception of *Brassica oleracea capitata*, *Lepidium sativum*, *Sinapis alba*, *Sinapis nigra*, and *Raphanus sativus* sprouts, harvested between the onset of germination up to and including the 2-leaf stage, or a non-toxic solvent extract of said sprouts.

69. The method according to claim 68, wherein said sprouts are harvested 1 to 14 days post-germination and have at least 200,000 units per gram fresh weight of Phase 2 enzyme-inducing potential when measured after 3-days of growth from seeds that produce said sprouts and non-toxic levels of indole glucosinolates and their breakdown products and goitrogenic hydroxybutenyl glucosinolates.

70. A method of reducing the level of carcinogens in a mammal, comprising administering to a mammal an effective amount of a food product comprising cruciferous sprouts, with the exception of *Brassica oleracea capitata*, *Lepidium sativum*, *Sinapis alba*, *Sinapis nigra*, and *Raphanus sativus* sprouts, harvested between the onset of germination up to and including the 2-leaf stage, or a non-toxic solvent extract of said food product.

Divisional of Serial No. 08/528,858
filed Sept. 15, 1995

71. The method according to claim 70, wherein said sprouts have at least 200,000 units per gram fresh weight of Phase 2 enzyme-inducing potential when measured after 3-days of growth from seeds that produce said sprouts and non-toxic levels of indole glucosinolates and their breakdown products and goitrogenic hydroxybutenyl glucosinolates and are harvested 1 to 14 days post-germination.--

A'cont

REMARKS

Claims 48-71 are pending in the application. Claims 1-47 have been canceled. New claims 48-71 have been added. Support for new claims can be found in the original claims and the specification as filed. Specifically, see Page 8, line 33 and Page 14, line 7.

Respectfully submitted,

Richard C. Peet
Registration No. 35,792

December 24, 1997
Date

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A
#13/B
DW 4/2/98

12/24/97 JC526 U.S. PTO

Assistant Commissioner for Patents
Box Patent Applications
Washington D.C. 20231

Attorney Docket No.046528/0116/JOHO
(must include alphanumeric codes if no inventors named)

UTILITY PATENT APPLICATION TRANSMITTAL
(new nonprovisional applications under 37 CFR 1.53(b))

Transmitted herewith for filing is the patent application of:

INVENTOR(S): Jed W. FAHEY, Paul TALALAY

TITLE: CANCER CHEMOPROTECTIVE FOOD PRODUCTS

In connection with this application, the following are enclosed:

08997813 - 122497

APPLICATION ELEMENTS:

XX Specification - 51 TOTAL PAGES

(preferred arrangement:)

-Descriptive Title of the Invention
-Cross Reference to Related Applications
-Statement Regard Fed sponsored R&D
-Reference to Microfiche Appendix
-Background of the Invention
-Brief Summary of the Invention
-Brief Description of the Drawings (if filed)
-Detailed Description
-Claim(s)
-Abstract of the Disclosure

XX Drawings - Total Sheets 2

XX Declaration and Power of Attorney - Total Sheets 2

_ Newly executed (original or copy)

XX Copy from a prior application (37 CFR 1.63(d))

(relates to continuation/divisional boxes completed) - NOTE: Box below

__ DELETION OF INVENTOR(S) - Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

XX Incorporation By Reference (useable if copy of prior application Declaration being submitted)

The entire disclosure of the prior application, from which a COPY of the oath or declaration is supplied as noted above, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

__ Microfiche Computer Program (Appendix)

__ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)

__ Computer Readable Copy
__ Paper Copy (identical to computer copy)
__ Statement verifying identify of above copies

ACCOMPANYING APPLICATION PARTS

XX Copy of Assignment Papers (cover sheet & document(s))
___ 37 CFR 3.73(b) Statement (when there is an assignee)
___ English Translation Document (if applicable)
XX Information Disclosure Statement (IDS) with PTO-1449.
XX Preliminary Amendment
XX Return Receipt Postcard (MPEP 503)
___ Small Entity Statement(s)

B

Utility Patent Appli ion Transmittal
Attorney Docket No. 528/0116/JOHO - Foley & L dner
Page 2

XX Statement file in prior application, status still proper and desired.
__ Certified Copy of Priority Document(s) with Claim of Priority (if foreign priority is claimed).
__ OTHER:

If a **CONTINUING APPLICATION**, check appropriate box and supply the requisite information:
__ Continuation X Divisional __ Continuation-in-part (CIP) of prior application Serial No. 08/528,858 .

XX Amend the specification by inserting before the first line the following sentence: --This application is a __ continuation, X divisional or __ continuation-in-part of application Serial No. 08/528,858 , filed September 15, 1995;.--

now U.S. Pat. 5,725,895

CORRESPONDENCE ADDRESS:
Foley & Lardner Address noted above.
Telephone: 202-672-5300
Fax Number: 202-672-5399

FEE CALCULATIONS: (Small entity fees indicated in parentheses.)

(1) For	(2) Number Filed	(3) Number Extra	(4) Rate	(5) Basic Fee $790 ($395)
Total Claims	24 - 20 =	4	x $22 (x $11)	44.00
Independent Claims	4 - 3 =	1	x $82 (x $41)	41.00
Multiple Dependent Claims			$270 ($135)	0
Assignment Recording Fee per property			$40	0
Surcharge Under 37 C.F.R. 1.16(e)			$130 ($65)	0
			TOTAL FEE:	$480.00

METHOD OF PAYMENT:
A check in the amount of the above TOTAL FEE is attached. If payment by check is NOT enclosed, it is requested that the Patent and Trademark Office advise the undersigned of the period of time within which to file the TOTAL FEE. If payment enclosed, this amount is believed to be correct; however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 19-0741.

Respectfully submitted,

Richard Post 35792
Bernhard D. Saxe
Reg. No. 28,665

Date: December 24, 1997
Docket No.: 046528/0116/JOHO

49

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

046528/0116/JOHO

In re patent application of

Jed FAHEY et al.

Serial No. UNKNOWN Group Art Unit: UNKNOWN

Filed: December 24, 1997 Examiner: UNKNOWN

For: CANCER CHEMOPROTECTIVE FOOD PRODUCTS

(Divisional of 08/528,858, filed September 15, 1995)

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. § 1.56

Honorable Assistant Secretary and
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Submitted herewith on Form PTO-1449 is a listing of documents known to Applicants in order to comply with applicants' duty of disclosure pursuant to 37 C.F.R. § 1.56.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). Applicants not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a prima facie prior art reference against the claims of the present application.

Divisional of 08/528,858
filed September 15, 1995

CONCISE EXPLANATION OF
RELEVANCE OF EACH DOCUMENT

Applicants are submitting herewith on Form PTO-1449, a listing of the documents cited by or submitted to the Patent Office in parent application Serial No. 08/528,858, filed September 15, 1995. The relevance of these prior art documents is explained in the parent application.

Since this Information Disclosure Statement is being filed in compliance with 37 C.F.R. §1.97(b) within three (3) months of the filing date, no fee is required in connection with its filing.

Applicants respectfully request that the listed documents be considered by the Examiner and be made of record in the present application and that an initialled copy of Form PTO-1449 be returned in accordance with M.P.E.P. § 609.

Respectfully submitted,

December 24, 1997

Richard C. Peet
Registration No. 35,792

FOLEY & LARDNER
3000 K Street, N.W.
Suite 500
Washington, D.C. 2007-5109
(202) 672-5300

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/997,813	12/24/97	FAHEY J	046528/0116/

HM42/0924

FOLEY & LARDNER
3000 K STREET NW
SUITE 500
WASHINGTON DC 20007-5109

EXAMINER	
JORDAN, K	

ART UNIT	PAPER NUMBER
1614	5

DATE MAILED: 09/24/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (REV. 2/95)

1-File Copy

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

Office Action Summary	Application No. 08/997,613	Applicant(s) Fahey et al.
	Examiner Kimberly Jordan	Group Art Unit 1814

☐ Responsive to communication(s) filed on _____.

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *48-71* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *48-55, 58-65, and 68-71* is/are rejected.

☒ Claim(s) *56, 57, 66, and 67* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

KIMBERLY JORDAN
PRIMARY EXAMINER
GROUP 1200
1610

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

U. S. Patent and Trademark Office
PTO-326 (Rev. 9-95) Office Action Summary Part of Paper No. 5

Claims 48-71 are presented for examination.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 48-55, 58-65, and 68-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cho et al. (A1). The claims appear to be drawn to a methods of increasing the chemoprotective amount of Phase 2 enzymes or reducing the level of carcinogens by administering cruciferous sprouts harvested by the 2-leaf stage. Cho et al. teaches compounds derived from *Brassica oleracea italica* to be potent selective inducers of Phase 2 enzymes which are useful chemoprotectants and detoxify carcinogens (see abstract; column 1, lines 10-16; column 3, line 24 - column 5, line 46). The claims differ from the cited reference in claiming administering sprouts harvested at a specific stage of growth. To administer the sprouts at the

stage of growth recited in the claims would have been obvious because the chemoprotective compounds contained in the sprouts are some of the same compounds disclosed by the reference to be extracted from *Brassica oleracea italica* and known to be chemoprotectants. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited reference.

Claims 56-57 and 66-67 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The remaining references listed on the enclosed PTO-1449 are cited to show the state of the art.

No claims are allowed.

Any inquiry concerning this communication should be directed to Kimberly Jordan at telephone number (703) 308-4611.

KIMBERLY JORDAN
PRIMARY EXAMINER
GROUP 1200-
1610

JORDAN

September 21, 1998

Sheet 1 of 2

FORM PTO 1449 (*modified*)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT(S)
(*Use several sheets if necessary*)

Date Submitted to PTO: December 24, 1997

ATTY DOCKET NO. 046528/0118/JOHO

SERIAL NO. DIV OF 08/628,858

APPLICANT FAHEY *et al.*

FILING DATE December 24, 1997

GROUP 1614

JC857 U.S. PTO 08/997813 12/24/97

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
LMJ	A1	5,411,986	5/95	CHO *et al.*	514	514	

OTHER DOCUMENT(S) (*Including Author, Title, Date, Pertinent Pages, Etc.*)

LMJ	A2	The Good New Sprouts Recipe Book, International Sprout Growers Association, pp. 1-8, August 1992.
	A3	Posner *et al.*, "Design and Synthesis of Bifunctional Isothiocyanate Analogs of Sulforaphane ... Detoxication Enzymes", *J. Med. Chem.* 37(1): 170-175 (1994)
	A4	Zhang *et al.*, "A Major Inducer of Anticarcinogenic Protective Enzymes... Structure", *Proc. Natl Acad. Sci. USA* 89: 2399-2403 (1992)
	A5	Prochaska *et al.*, "Rapid Detective of Inducers of Enzymes That Protect Against Carcinogens", *Proc. Natl Sci. USA* 89: 2394-2398 (1992)
	A6	Zhang *et al.*, "Anticarcinogenic Activities of Sulforaphane and Structurally Related Synthetic Norbornyl Isothiocyanates", *Proc. Natl Sci. USA* 91: 3147-3150 (1994)
	A7	Prochaska *et al.*, "Regulatory Mechanisms of Monofunctional...In Murine Liver", *Cancer Research* 48: 4776-4782 (1988)
	A8	Prochaska *et al.*, "Direct Measurement of NAD(P)H: Quinone Reductase from Cells Cultured...Inducers", *Analytical Biochemistry* 169: 328-336 (1988)
	A9	Beecher, "Cancer Prevention Properties of Varieties of Brassica Oleracea: A Review...", *Am. J. Clin. Nutr.* 59(Suppl): 1166s-1170s (1994)
	A10	Prestera *et al.*, "Chemical and Molecular Regulation of Enzymes that Detoxify Carcinogens", *Proc. Natl Acad. Sci. USA* 90: 2965-2969 (1993)
	A11	Zhang *et al.*, "Anticarcinogenic Activities of Organic Isothiocyanates: Chemistry and Mechanisms", *Cancer Research suppl* 54: 1976s-1981s (1994)
	A12	Talalay, "The Role of Enzyme Induction in Protection Against Carcinogenesis", *Cancer Chemoprevention*, pp 469-478 (1992)
LMJ	A13	Prestera *et al.*, "The Electrophile Counterattack Response: Protection Against Neoplasia and Toxicity", *Advan. Enzyme Regul.* 33: 281-296 (1993)

EXAMINER [signature] DATE CONSIDERED 9/21/98

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

IPT-212(a):4/90

Sheet 2 of 2

FORM PTO 1449 (modified) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary) Date Submitted to PTO: December 24, 1997	ATTY DOCKET NO. 046528/0118/JOHO	SERIAL NO. DIV OF 08/528,858
	APPLICANT FAHEY et al.	
	FILING DATE December 24, 1997	GROUP 1614

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

OTHER DOCUMENT(S) (Including Author, Title, Date, Pertinent Pages, Etc.)

KG	A14		Masilungan et al., "Screening of Philippine Medicinal Plants for Anticancer Agents Using CCNSC Protocols", *Cancer Chemotherapy Reports (Part 2)* 2(1): 135-140 (April 1971)
KG	A15		Polasa et al., "Cancer Preventive Properties of Varieties of Brassica Oleracea: A Review Source", *Am. J. of Clinical Nutrition* 59(5): (1994)
KG	A16		Patent Abstract of Japan Sect. No. 305, Vol. 9, No. 2371, p.2 (Sept. 1985)
KG	A17		Barrett et al., "Protective Effect f Cruciferous Seed Meals Against Mouse Colon Cancer", *Cereal Food World* 39(8): 613 (August 1994)

[signature] 9/21/98

IPT-212(a):4/90

FORM PTO 948 (REV. 11-97) U.S. DEPARTMENT OF COMMERCE-Patent and Trademark Office Application No. 997813

NOTICE OF DRAFTPERSON'S PATENT DRAWING REVIEW

The drawing filed (insert date) 12/24/97 are:

A. X not objected to by the Draftperson under 37 CFR 1.84 or 1.152.

B. _____ objected to by the Draftperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink. Color.
   - _____ Color drawing are not acceptable until petition is granted. Fig.(s) _____
   - _____ Pencil and non black ink is not permitted. Fig(s)_____
2. PHOTOGRAPHS. 37 CFR 1.84(b)
   - _____ Photographs are not acceptable until petition is granted.
   - _____ 3 full-tone sets are required. Fig(s)_____
   - _____ Photographs not properly mounted (must brystol board or photographic double-weight paper). Fig(s)_____
   - _____ Poor quality (half-tone). Fig(s)_____
3. TYPE OF PAPER. 37 CFR 1.84(e)
   - _____ Paper not flexible, strong, white and durable. Fig.(s)_____
   - _____ Erasures, alterations, overwritings, interlineations, folds, copy machine marks not acceptable. (too thin)
   - _____ Mylar, vellum paper is not acceptable (too thin). Fig(s)_____
4. SIZE OF PAPER. 37 CFR 1.84(F): Acceptable sizes:
   - _____ 21.0 cm by 29.7 cm (DIN size A4)
   - _____ 21.6 cm by 27.9 cm (8 1/2 x 11 inches)
   - _____ All drawings sheets not the same size. Sheet(s)_____
5. MARGINS. 37 CFR 1.84(g): Acceptable margins:
   - Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm SIZE: A4 Size
   - Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm SIZE: 8 1/2 x 11
   - _____ Margins not acceptable. Fig(s)_____
   - _____ Top (T) _____ Left (L)
   - _____ Right (R) _____ Bottom (B)
6. VIEWS. CFR 1.84(h)
   REMINDER: Specification may require revision to correspond to drawing changes.
   - _____ Views connected by projection lines or lead lines. Fig.(s)_____

   Partial views. 37 CFR 1.84(h)(2)
   - _____ Brackets needed to show figure as one entity. Fig.(s)_____
   - _____ Views not labeled separately or properly. Fig.(s)_____
   - _____ Enlarged view not labeled separately or properly. Fig.(s)_____
7. SECTIONAL VIEWS. 37 CFR 1.84(h)(3)
   - _____ Hatching not indicated for sectional portions of an object. Fig.(s)_____
   - _____ Sectional designation should be noted with Arabic or Roman numbers. Fig.(s)_____
8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   - _____ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned, so that the top becomes the right side, except for graphs. Fig.(s)_____
   - _____ Views not on the same plane on drawing sheet. Fig.(s)_____
9. SCALE. 37 CFR 1.84(k)
   - _____ Scale not large enough to show mechansim without crowding when drawing is reduced in size to two-thirds in reproduction. Fig.(s)_____
10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
    - _____ Lines, numbers & letters not uniformly thick and well defined, clean, durable and black (poor line quality). Fig.(s)_____
11. SHADING. 37 CFR 1.84(m).
    - _____ Solid black areas pale. Fig.(s)_____
    - _____ Solid black shading not permitted. Fig.(s)_____
    - _____ Shade lines, pale, rough and blurred. Fig.(s)
12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.48(p)
    - _____ Numbers and reference characters not plain and legible. Fig.(s)_____
    - _____ Figure legends are poor. Fig.(s)_____
    - _____ Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(3) Fig.(s)_____
    - _____ Engligh alphabet not used. 37 CFR 1.84(p)(3) Fig.(s)_____
    - _____ Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3) Fig.(s)_____
13. LEAD LINES. 37 CFR 1.84(q)
    - _____ Lead lines cross each other. Fig.(s)_____
    - _____ Lead lines missing. Fig.(s)_____
14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.48(t)
    - _____ Sheets not numbered consecutively, and in Ababic numerals beginning with number 1. Fig.(s)_____
15. NUMBERING OF VIEWS. 37 CFR 1.84(u)
    - _____ Views not numbered consecutively, and in Abrabic numerals, beginning with number 1. Fig.(s)_____
16. CORRECTIONS. 37 CFR 1.84(w)
    - _____ Corrections not made from PTO-948 dated _____
17. DESIGN DRAWINGS. 37 CFR 1.152
    - _____ Surface shading shown not appropriate. Fig.(s)_____
    - _____ Solid black shading not used for color contrast. Fig.(s)_____

COMMENTS

REVIEWER W.D DATE 3/17/98 TELEPHONE NO. 7033058404

ATTACHMENT TO PAPER NO. 4

PTO COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Group Art Unit:	1614
Jed FAHEY et al.	:	Examiner:	K. Jordan
Serial No.: 08/997,813	:	Atty. Dkt. No.	46585/116
Filed: December 24, 1997:			
For: CANCER CHEMOPROTECTIVE FOOD PRODUCTS			

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§1.56, 1.97(c) and 1.17(p)

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Included with the attached Form PTO-1449 is a document known to applicants in order to comply with applicants' duty of disclosure pursuant to 37 C.F.R. § 1.56.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or is considered to be material to patentability as defined in 37 C.F.R. §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* prior art reference against the claims of the present application.

Applicants respectfully request that this document be considered and made of record in the present application and that an initialled copy of form PTO-1449 be returned in accordance with M.P.E.P. §609.

Applicants submit this document under 37 C.F.R. §1.97(e), before the mailing date of either a final action under §1.113 or of a Notice of Allowance under §1.311. Accordingly, the fee set forth in §1.17(p) of $240 is attached, and it is believed that no additional fees are required. However, the Commissioner is hereby authorized to charge any deficiency or to credit any overpayment to Deposit Account No. 19-0741.

January 11, 1999
Date

Respectfully submitted,

Richard C. Peet
Reg. No. 35,792

FOLEY & LARDNER
3000 K Street, NW, Suite 500
Washington, DC 20007-5109
(202) 672-5300

1614 $

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 046528/0116/JOHO

#7
2/18/99

In re patent application of
Jed FAHEY et al.
Serial No. 08/997,813
Filed: December 24, 1997
For: CANCER CHEMOPROTECTIVE FOOD PRODUCTS

Group Art Unit: 1614
Examiner: K. Jordan

OIPE JAN 25 1999 PATENT & TRADEMARK OFFICE 2900

PETITION FOR EXTENSION OF TIME
UNDER 37 C.F.R. § 1.136

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

It is respectfully requested that an extension of time for the period indicated below be granted in accordance with the provisions of 37 C.F.R. § 1.136 to take the action required in the application identified in caption, as reflected by the papers submitted herewith.

XX	First Month	$110	($ 55)*	
____	Second Month	$270	($135)*	
____	Third Month	$490	($245)*	
____	Fourth Month	$490	($245)*	
____	Fifth Month	$490	($245)*	
* *(Small Entity)*	TOTAL FEE:	$110.00		

01 FC:115 110.00 OP

A check in the amount of the above Total Fee is attached. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 19-0741. If one or more (additional) extension(s) of time is/are required for the filing of this paper, such extension(s) is/are hereby expressly petitioned for and the Commissioner is authorized to charge the required fee to Deposit Account No. 19-0741.

02/01/1999 HMARMOL 00000101 08997813

Respectfully submitted,

for Richard C. Peet (28,665)
Richard C. Peet
Reg. No. 35,792

January 25, 1999
Date

FOLEY & LARDNER
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 046528/0116/JOHO

#8/C JRR 2/18/99

In re patent application of
Jed FAHEY et al.
Serial No. 08/997,813
Filed: December 24, 199
For: CANCER CHEMOPROTECTIVE FOOD PRODUCTS

Group Art Unit: 1614
Examiner: K. Jordan

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. § 1.111

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action mailed September 24, 1998, please amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel claims 58-67 and 70-71 without prejudice or disclaimer.

Please amend the claims as follows:

~~48~~. A method of increasing the chemoprotective amount of Phase 2 enzymes in a mammal, comprising the [step of administering to a mammal an effective quantity of cruciferous sprouts, with the exception of *Brassica oleracea capitata*, *Lepidium sativum*, *Sinapis alba*, *Sinapis nigra*, and *Raphanus sativus* sprouts, harvested between the onset of germination up to and including the 2-leaf stage, or a non-toxic solvent extract of said sprouts] steps of:

C1

(a) identifying seeds which produce cruciferous sprouts, with the exception of *Brassica oleracea capitata*, *Lepidium sativum*, *Sinapis alba*, *Sinapis nigra*, and *Raphanus sativus* sprouts, containing high Phase 2 enzyme-inducing potential and non-toxic levels of indole glucosinolates and their breakdown products and goitrogenic hydroxybutenyl glucosinolates;

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(b) germinating said seeds;

(c) harvesting said sprouts between the onset of germination up to and including the 2-leaf stage to form a food product comprising a plurality of sprouts; and

(d) administering said food product, or a non-toxic extract of said food product, to said mammal.

~~10~~. A method of reducing the level of carcinogens in a mammal, comprising [administering to a mammal an effective amount of cruciferous sprouts, with the exception of *Brassica oleracea capitata*, *Lepidium sativum*, *Sinapis alba*, *Sinapis nigra*, and *Raphanus sativus* sprouts, harvested between the onset of germination up to and including the 2-leaf stage, or a non-toxic solvent extract of said sprouts] the steps of:

(a) identifying seeds which produce cruciferous sprouts, with the exception of *Brassica oleracea capitata*, *Lepidium sativum*, *Sinapis alba*, *Sinapis nigra*, and *Raphanus sativus* sprouts, containing high Phase 2 enzyme-inducing potential and non-toxic levels of indole glucosinolates and their breakdown products and goitrogenic hydroxybutenyl glucosinolates;

(b) germinating said seeds;

(c) harvesting said sprouts between the onset of germination up to and including the 2-leaf stage to form a food product comprising a plurality of sprouts; and

(d) administering said food product, or a non-toxic extract of said food product, to said mammal.

Please add the following new claims:

~~72~~. The method according to claim ~~69~~, wherein said seeds produce cruciferous sprouts containing at least 200,000 units per gram fresh weight of Phase 2 enzyme-inducing potential measured after 3-days of growth.

~~73~~. The method according to claim ~~69~~, wherein said seeds produce cruciferous sprouts containing at least 300,000 units per

gram fresh weight of Phase 2 enzyme-inducing potential measured after 3-days of growth.

~~74~~ 5. The method according to claim ~~49~~ 2, wherein said seeds produce cruciferous sprouts containing at least 400,000 units per gram fresh weight of Phase 2 enzyme-inducing potential measured after 3-days of growth.

~~75~~ 6. The method according to claim ~~49~~ 2, wherein said seeds produce cruciferous sprouts containing at least 500,000 units per gram fresh weight of Phase 2 enzyme-inducing potential measured after 3-days of growth.

~~76~~ 7. The method according to claim ~~49~~ 2, wherein said seeds produce cruciferous sprouts containing at least 200,000 units per gram fresh weight of Phase 2 enzyme-inducing potential measured after 3-days of growth.

C13 cont.

~~77~~ 15. The method according to claim ~~69~~ 17, wherein said seeds produce cruciferous sprouts containing at least 300,000 units per gram fresh weight of Phase 2 enzyme-inducing potential measured after 3-days of growth.

~~78~~ 19. The method according to claim ~~69~~ 17, wherein said seeds produce cruciferous sprouts containing at least 400,000 units per gram fresh weight of Phase 2 enzyme-inducing potential measured after 3-days of growth.

~~79~~ 20. The method according to claim ~~69~~ 17, wherein said seeds produce cruciferous sprouts containing at least 500,000 units per gram fresh weight of Phase 2 enzyme-inducing potential measured after 3-days of growth.

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REMARKS

Claims 58-67 and 70-71 are canceled without prejudice or disclaimer. Claims 48 and 68 are amended and claims 72-78 are added. Support for the amendments to claims 48 and 68 and new claims 72-79 is found in the originally presented claims and throughout the specification, for example, pages 14-15, 18 and 20. Claims 48-57, 68-69 and 72-78 are pending and presented for examination.

Claims 48-55, 58-65 and 68-71 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,411,986 ("the '986 patent"). The '986 patent identifies broccoli (*Brassica oleracea* var. *italica*) as a source of the Phase 2 enzyme inducer sulforaphane. Dr. Paul Talalay avers in the accompanying declaration, attached hereto as APPENDIX A, that he is one of the named inventors of the '986 patent and that this patent teaches that broccoli is a source of sulforaphane (See examples 2 and 3). The '986 patent fails to teach or suggest that broccoli sprouts, or other cruciferous sprouts, contain high concentrations of Phase 2 inducer activity. Accordingly, the examiner has failed to set forth a *prima facie* case of obviousness.

Even assuming the examiner had set forth a *prima facie* case of obviousness, clear evidence of unexpected results contained in the specification has been overlooked. Proof of an unexpected improvement can rebut a *prima facie* case of obviousness. *In re Costello*, 480 F.2d 894, 178 USPQ 290 (CCPA 1973). Specifically, the methods of the instant invention provide food products that have unexpected health benefits compared to food products available in the prior art.

More specifically, the claimed methods of the instant application provide food products comprised of certain cruciferous sprouts, and sprout extracts, with greatly increased

levels of Phase 2 inducer activity compared to mature market stage vegetables. As a consequence, a significant health benefit can be realized through ingestion of small quantities of cruciferous sprouts, or sprout extracts, prepared according to the claimed methods. The same health benefits can only be realized, if at all, through the ingestion of impractically large quantities of market stage vegetables that contain significantly lower concentrations of anticarcinogenic Phase 2 inducer activity compared to the sprouts of the instant invention.

Phase 2 enzymes conjugate functionalized products with endogenous ligands (*e.g.*, glutathione, glucuronic acid, sulfate) and thereby serve primarily a detoxifying role in xenobiotic metabolism. There is very good evidence indicating that when Phase 2 enzymes are induced, animals and cells are protected against the toxic and neoplastic effects of carcinogens. In fact, anticarcinogens have been identified based on their ability to induce Phase 2 enzymes. *See*, for example, Talalay, Paul, *Chemical Protection Against Cancer by Induction of Electrophile Detoxification (Phase II) Enzymes*, In: CELLULAR AND MOLECULAR TARGETS OF CHEMOPREVENTION, V.E. Steele *et al.*, (eds.), CRC Press, Boca Raton, Florida (1992).

The ability of Phase 2 enzyme inducers, such as isothiocyanates, to block carcinogenesis has been known for many years. *See*, for example, Zhang *et al.*, *Cancer Research* 54 (Suppl): 1976-1981S (1994). In addition, numerous epidemiological studies suggest that high consumption of yellow and green vegetables, especially those of the family Cruciferae and the genus *Brassica* such as cauliflower, cabbage or broccoli reduces the risk of developing cancer of various organs. *See*, for example, Graham *et al.*, *J. Natl. Cancer Inst.* 61: 709-714 (1978). However, the quantity of mature market stage vegetables that must be consumed in order to provide even a 50% reduction

in cancer risk ratio is so very large as to be difficult for many individuals and further risk reduction is impractical.

Dr. Talalay notes in the accompanying Rule 132 Declaration, attached hereto as Appendix A that consumption of 425 g/wk of mature market stage *Brassica* vegetables, such as broccoli, would result in an odds ratio of approximately 0.5 (50% risk reduction) for colon cancer. It is frequently impractical and many individuals cannot tolerate consumption of such a large quantity of market stage broccoli each week. The large quantity of fiber and other phytochemicals associated with the consumption of such large quantities of this vegetable is likely to cause bowel irritation and/or flatulence in a significant portion of the population. In addition, many individuals dislike the taste of cruciferous vegetables and will not consume such large quantities for this reason.

Cruciferous sprouts prepared according to the instant invention provide 20 to 50-fold higher levels of Phase 2 enzyme inducer activity than mature, market stage cruciferous vegetables (see Appendix A1). Accordingly, much smaller quantities of the sprouts can be consumed to realize the same health benefit obtained through consumption of larger quantities of mature market stage vegetables. Dr. Talalay in the accompanying Rule 132 Declaration calculates that 3 grams of 3-day old sprouts, or 150 milligrams of lyophilized hot water extract of sprouts, contain the same quantity of Phase 2 inducer activity as 150 grams of mature market stage broccoli. The quantity of mature market stage broccoli, sprouts and sprout extracts that must be consumed to realize the same health benefit (2-1/4 million units of anticarcinogen Phase 2 enzyme inducer activity) is shown in Appendix A2 attached to Dr. Talalay's Rule 132 Declaration.

Another unrecognized and unexpected benefit of the claimed methods is to provide food products comprised of certain

cruciferous spouts and sprout extracts that do not contain significant levels of Phase 1 inducer activity, derived from indole glucosinolates. Phase 1 enzymes (cytochromes P-450) functionalize compounds, usually by oxidation or reduction. Although one role of Phase 1 enzymes is to detoxify xenobiotics, **several cytochromes P-450 activate various types of procarcinogens to highly reactive ultimate carcinogens.**

Attached to Dr. Talalay's Rule 132 Declaration as Appendix A3 are graphs showing comparative paired ion chromatographs of broccoli sprouts and mature market stage broccoli. The paired ion chromatographs were prepared according to the method developed in his laboratory by Prestera *et al.*, *Anal. Biochem.* 239: 168-179 (1996). The principal peaks are glucoraphanin, glucoerucin, glucobrassicin and neoglucobrassicin (Appendix A3) The former two glucosinolates are alkythioglucosinolates with potent Phase 2 enzyme inducer activity and are the predominant glucosinolates found in sprouts. The latter two glucosinolates are indole glucosinolates which predominate in mature market stage broccoli. The indole glucosinolates are (1) very weak Phase 2 enzyme inducers; (2) are bifunctional inducers and therefore induce both Phase 1 and Phase 2 enzymes; (3) degrade to produce products which bind to the Ah receptor and induce certain cytochromes P-450 that activate carcinogens; and (4) may actually enhance carcinogenic activity. Accordingly, the methods of the instant application provide food products that not only contain unexpectedly high levels of anticarcinogenic Phase 2 inducer activity but also contain unexpectedly low levels of carcinogenic Phase 1 enzyme inducer activity.

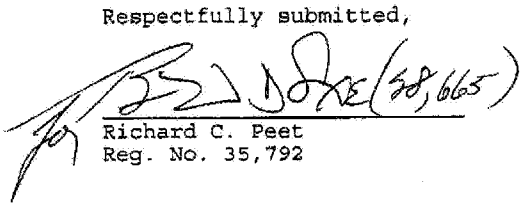
The prior art does not teach or suggest methods for increasing the chemoprotective amount of Phase 2 enzymes in a mammal or reducing the level of carcinogens in a mammal. Accordingly, the examiner has failed to set forth a *prima facie* case of obviousness. Although unnecessary to overcome the

examiner's obviousness rejection because of the lack of a *prima facie* case of obviousness, evidence of totally unexpected results is presented. The claimed methods of the instant application provide food products comprised of certain cruciferous sprouts, and sprout extracts, with greatly increased levels of Phase 2 inducer activity compared to mature market stage vegetables. Additionally, food products prepared according to the claimed invention do not contain significant levels of Phase 1 inducer activity which may actually enhance carcinogenic activity.

It is therefore respectfully urged that the claims are not obvious over the prior art cited by the examiner and the rejection should be withdrawn.

In view of the amendments to the claims and the foregoing remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions concerning this application, Examiner Jordan is urged to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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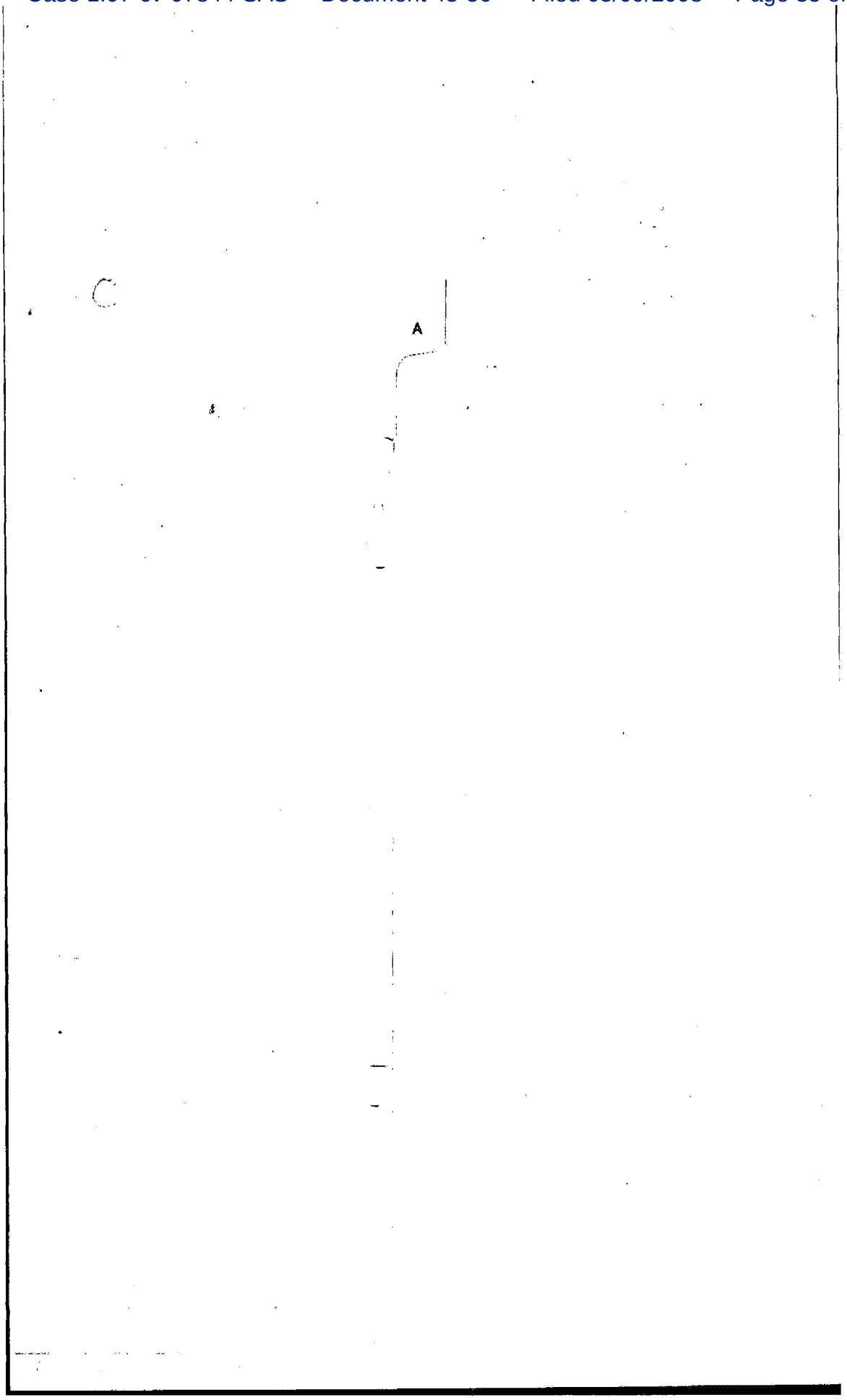

A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No. 046585/0116

In re patent application of
Jed FAHEY *et al.*
Serial No. 08/997,813
Filed: April 11, 1997
For: CANCER CHEMOPROTECTIVE FOOD PRODUCTS

DECLARATION OF PAUL TALALAY
UNDER 37 C.F.R. §1.132

I, Paul Talalay, being duly warned, hereby declare and say:

1. I am a citizen of the United States of America, and reside at 5512 Boxhill Lane, Baltimore, MD 21210.

2. I am John Jacob Abel Distinguished Service Professor, Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205. I am a member of the National Academy of Sciences of the United States, a Member of the American Philosophical Society founded in Philadelphia for the promotion of useful knowledge, and a former Professor of the American Cancer Society.

3. I am a physician and medical scientist who has been involved for the last 20 years in devising chemical and dietary strategies for reducing the risk of human cancer.

4. I am a co-inventor named in U.S. application serial No. 08/997,813 ("the application"). In relation to the application, I have reviewed an Official Action, mailed September

24, 1998, and the prior art cited therein, and I make the following observations.

5. I am a named inventor of U.S. Patent No. 5,411,986 ("the '986 patent"). The Examiner asserts that the claims of the instant application are obvious over the teachings of the '986 patent. However, the '986 patent fails to teach or suggest that broccoli sprouts, or other cruciferous sprouts, are a source of sulforaphane or phase 2 enzyme inducer activity.

6. Examples 2 and 3 of the '986 patent teach that broccoli is a source of sulforaphane. Market stage, mature broccoli was used in the experiments described in Examples 2 and 3 of the '986 patent. The '986 patent therefore fails to teach or suggest that broccoli sprouts, or other cruciferous sprouts are a source of sulforaphane or Phase 2 inducer activity. In fact, we were extremely surprised to subsequently find that broccoli and other cruciferous sprouts contain high concentrations of Phase 2 enzyme inducer activity.

7. The claimed methods of the application provide food products that not only contain unexpectedly high levels of anticarcinogenic Phase 2 inducer activity, but also contain unexpectedly low levels of potentially carcinogenic Phase 1 enzyme inducer activity. The prior art reference relied on by the examiner does not teach or suggest these unexpected

attributes of the human food product made by the claimed methods. The sprouts and their extracts are therefore both qualitatively and quantitatively radically different in their content of enzyme inducer activities compared to mature, market stage vegetables.

8. There is a continuing proliferation of epidemiological studies that demonstrate an inverse relation between the *quantity* of vegetables consumed and the risk of cancer. Furthermore, several of these studies emphasize the protective effect of cruciferous vegetables, specifically, and demonstrate a *dose dependence* of the magnitude of the effect. Consumption of >425 g/wk of mature, market stage *Brassica* sp. reduces the cancer odds ratio to approximately 0.5 (50% risk reduction) for colon cancer in comparison to the consumption of <125 g/wk. Kune et *al.*, *Nutr. Cancer* 9: 21-42 (1987). The odds ratios for colon cancer in relation to vegetable consumption was determined. Graham et *al.*, *J. Natl. Cancer Inst.* 61: 709—714 (1978). Individuals who ate an average of 0-20, 21-40, 41-60 and more than 61 servings per month had odds ratios of 1.00, 0.66, 0.57 and 0.47 respectively. If one extrapolates the results of Graham, a 75% reduction in cancer risk would require consumption of perhaps 750 g (ca. 1.5 lbs.) of vegetables per day. The results of 7 cohort studies and 87 case—control studies have been summarized. See Verhoeven *et al.*, *Cancer Epid. Biomarkers & Preventions* 5: 733— 748 (1996). Cohort studies showed: inverse associations between the consumption of cabbage, cauliflower and broccoli and risk of lung cancer;

between consumption of brassica vegetables and risk of stomach cancer; between broccoli consumption and risk of all cancers taken together and between brassica consumption and the occurrence of second primary cancers. They conclude that a high consumption of brassica vegetables is associated with a decreased risk of cancer.

9. It is impractical for most individuals to consume the large quantities of market stage broccoli or other vegetables to achieve maximum protection, because the quantity of fiber and other phytochemicals that need to be consumed can cause bowel irritation and/or flatulence.

10. Cruciferous sprouts and sprout extracts prepared according to the claimed methods provide 20 to 50-fold higher levels of Phase 2 enzyme inducer activity than mature market stage cruciferous vegetables. The data from Tables 1 and 3 of the application are summarized in APPENDIX A1 attached hereto. A significant health benefit can be realized through ingestion of small quantities of cruciferous sprouts, or sprout extracts, prepared according to the claimed methods. The same health benefits can only be realized, if at all, through the ingestion of intolerably large quantities of market stage vegetables that contain significantly lower concentrations of anticarcinogenic Phase 2 inducer activity compared to the sprouts prepared according to the application.

11. For purposes of illustration, we determined in one experiment that 3 grams of 3-day old broccoli sprouts, or 150 milligrams of a lyophilized hot water extract made from 3-day old broccoli sprouts, contain the same quantity of Phase 2 enzyme inducer activity as 150 grams of mature market stage broccoli. Phase 2 enzyme inducer activity is measured in the Hepa 1c1c7 murine hepatoma cells grown in 96-well microtiter plates according to the method of Prochaska *et al.*, *Anal. Biochem.* 169: 328-336 (1988). One unit of Phase 2 enzyme inducer activity is defined as the amount that when added to a single microtiter well, doubles the quinone reductase activity. The quantity of mature market stage broccoli, sprouts and sprout extracts that must be consumed to realize the same health benefit (2-1/4 million units of anticarcinogenic Phase 2 enzyme inducer activity) is shown in APPENDIX A2 attached hereto.

12. The methods of the application also provide food products comprised of certain cruciferous sprouts and sprout extracts that do not contain significant levels of indole glucosinolates which generate Phase 1 inducers. Phase 1 enzymes (cytochromes P-450) functionalize compounds, usually by oxidation or reduction. Although one role of Phase 1 enzymes is to detoxify xenobiotics, several cytochromes P-450 activate procarcinogens to highly reactive ultimate carcinogens.

13. Attached hereto as APPENDIX A3 are graphs showing comparative paired ion chromatographs of broccoli sprouts and mature market stage broccoli. The paired ion chromatographs were prepared according to the method developed in our laboratory by Prestera *et al.*, *Anal. Biochem.* 239: 168–179 (1996). Shaded peaks on the chromatograph represent glucoraphanin, glucoerucin, glucobrassicin and neoglucobrassicin, respectively. The former two glucosinolates are alkylthioglucosinolates with potent Phase 2 enzyme inducer activity and are the predominant glucosinolates found in sprouts. The latter two glucosinolates are indole glucosinolates which predominate in mature market stage broccoli.

14. Recent studies have shown that sulforaphane (the hydrolysis product of glucoraphanin which is the principal inducer precursor in sprouts) has a number of favorable properties with respect to its use as a chemoprotector. Sulforaphane inhibits mammary tumor formation in female Sprague-Dawley rats treated with single doses of dimethylbenzanthracene. Zhang *et al.*, *Proc. Natl. Acad. Sci. USA* 91: 3147-3150 (1994). Sulforaphane shows exceedingly potent inhibitory activity against DMBA-induced neoplastic mammary lesions in mouse mammary gland explants in culture: 84, 56, and 34% inhibition at 1 μM, 100 nM, and 10 nM concentrations, respectively. Gerhauser et *al.*, *Cancer Research* 57: 272–278 (1997). Sulforaphane is not itself genotoxic (*i.e.*, does not produce unscheduled DNA synthesis) but inhibits the genotoxicity of N-nitrosodimethylamine (NDMA) in *Salmonella*

typhimurium and NDMA-induced unscheduled DNA synthesis in mouse hepatocytes. Barcelo et *al.*, *Carcinogenesis* 17: 277–282 (1996). Sulforaphane has the unusual property of inhibiting cytochrome P-450 type 2E1 which is involved in the metabolic activation of carcinogenic nitrosamines. Barcelo et *al.*, *Carcinogenesis* 17: 277–282 (1996).

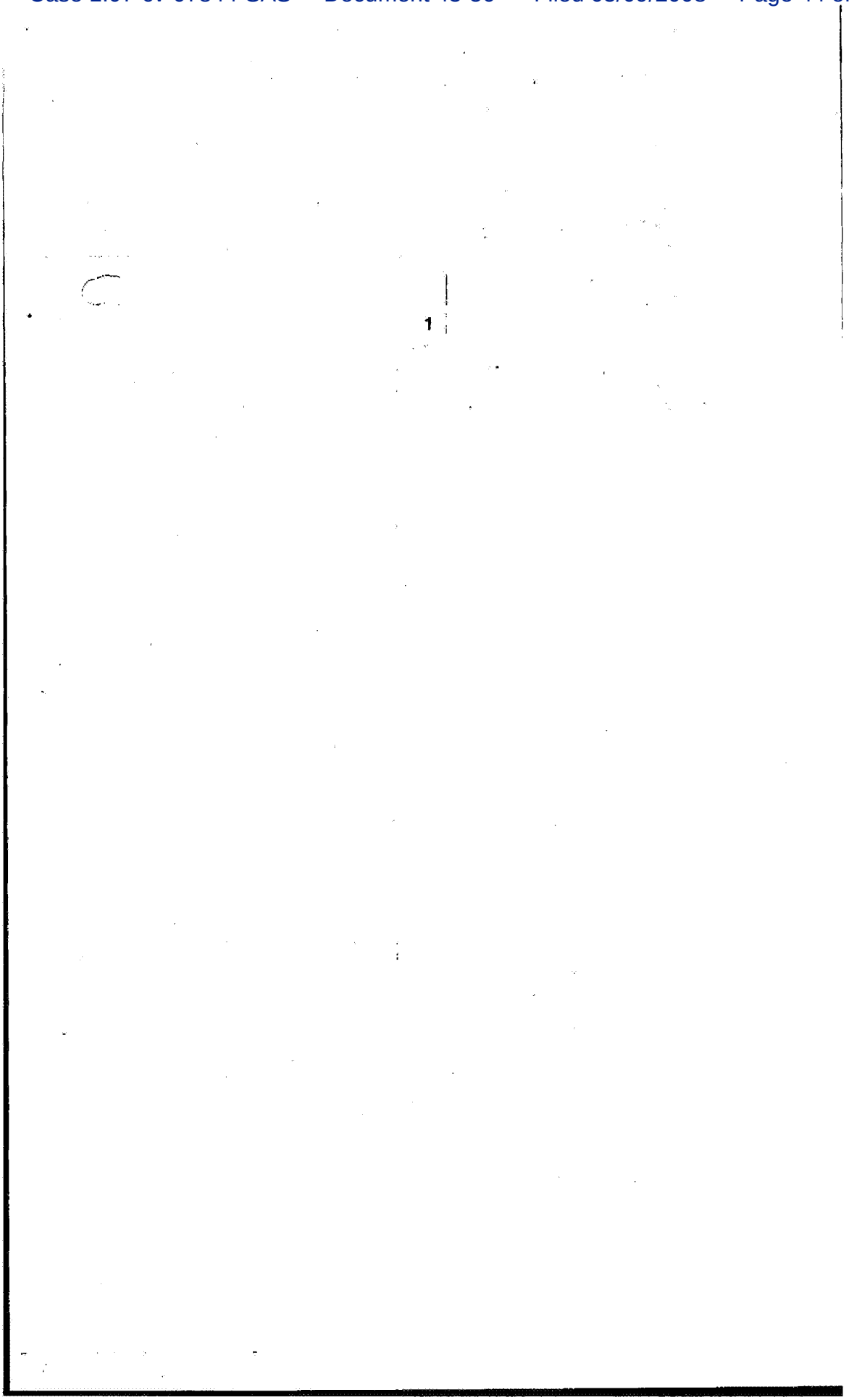
15. The indole glucosinolates do not give rise to isothiocyanates upon myrosinase hydrolysis because the indole isothiocyanates are unstable. One major degradation product is indole-3-carbinol which has attracted a great deal of recent attention. Although this compound exerts anticarcinogenic activity in some experimental tumor systems when administered before the carcinogen, it has obvious tumor-promoting properties if given after the carcinogen. Indole-3-carbinol has a number of other undesirable properties that raise questions with respect to the advisability of its use in chemoprotection. Thus, indole-3-carbinol is: (1) a very weak Phase 2 enzyme inducer; (2) is converted (especially at the acid pH prevailing in the stomach) to dimeric and trimeric condensation products that bind with very high affinity to the Ah receptor and thereby induce certain cytochromes P-450 that activate carcinogens, i.e., it is a bifunctional inducer that elevates both Phase 1 and Phase 2 enzymes; and (3) upon chronic administration indole-3-carbinol enhances carcinogenic activity. Such continuous administration represents a likely scenario in any chemoprotective strategy, and

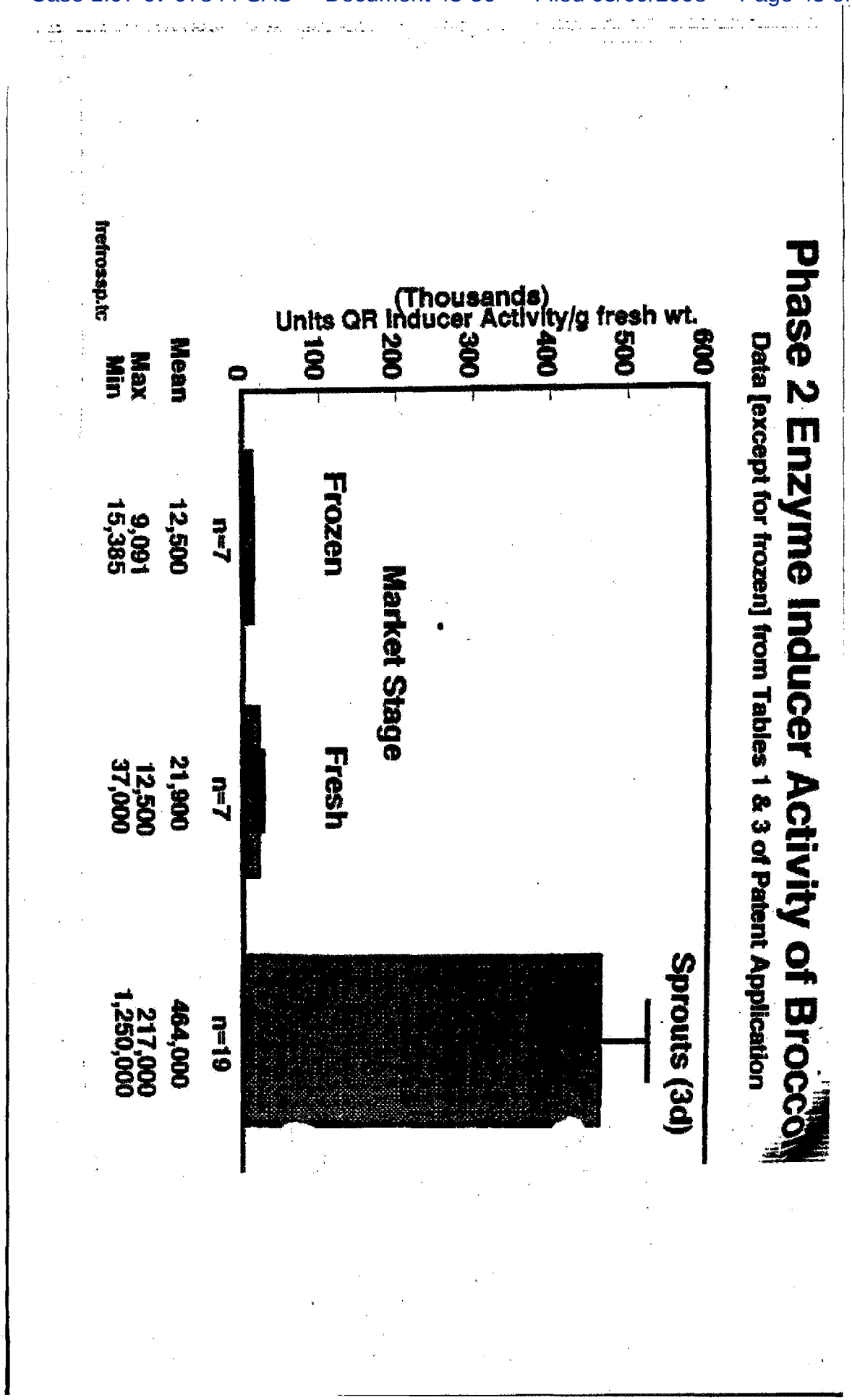
indole glucosinolates are therefore not very desirable agents for these purposes.

16. The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Date

Paul Talalay

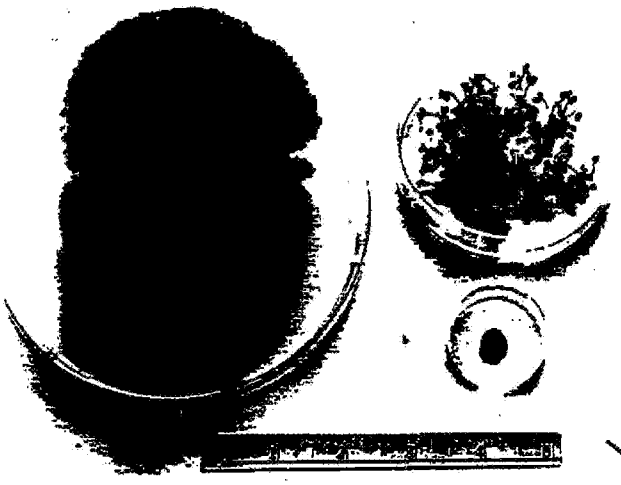



Phase 2 Enzyme Inducer Activity of Broccoli
Data [except for frozen] from Tables 1 & 3 of Patent Application
(Thousands)
Units QR Inducer Activity/g fresh wt.
0
100
200
300
400
500
600
Sprouts (3d)
Fresh
Frozen
Market Stage
n=19
n=7
n=7
Mean
Max
Min
464,000
217,000
1,250,000
21,900
12,500
37,000
12,500
9,091
15,385
frefrossp.tc

BROCCOLI

MARKET STAGE
(150 GRAMS)

3-DAY SPROUTS
(3 GRAMS)



FREEZE DRIED WATER EXTRACT
OF 3-DAY SPROUTS
(150 MG)

ALL PREPARATIONS CONTAIN THE SAME QUANTITY
(2-1/4 MILLION UNITS) OF ANTICARCINOGENIC
ENZYME INDUCER ACTIVITY

FIGURE 1

3

PAIRED ION CHROMATOGRAPHY SHOWING GLUCOSINOLATE PROFILES OF BROCCOLI (cv. SAGA)